

WHAT IS CLAIMED IS:

1. A method for production of a derivatized resin represented by the formula (I):
- (I)  $R_4-NH-(C=X)-Y-Z-SS$  wherein:
- $R_4$  is  $-NH-R_3$ ,  $-NH_2$ ,  $-OH$ , or  $-O-R_3$ , wherein  $R_3$  is a protecting group, provided that when  $R_4$  is  $-NH-R_3$  or  $-O-R_3$ , then the protecting group is removed and replaced by  $-H$  in the final product (I);
- $X$  is  $O$ ,  $S$ , or  $NR_7$ ;
- $R_7$  is  $H$ , alkyl, alkenyl, aryl, aralkyl, cycloalkyl, or heterocycle;
- $Y$  is absent,  $-NH-$ , or  $-CH_2-$ ;
- $Z$  is absent or is a substituent selected from the group consisting of  $-NH-$ ,  $-O-$ ,  $-(C=O)-$ ,  $-S-$ ,  $SO_2-$ , alkyl, alkenyl, aryl, aralkyl, cycloalkyl, heterocycle, and combinations thereof, provided that when  $Y$  is absent and  $X$  is  $O$  or  $S$ ,  $Z$  does not comprise  $-(C=O)-$  immediately adjacent to  $-(C=X)-$ , and when  $Y$  is  $-NH-$  and  $Z$  comprises an  $-NH-$  or an  $-S-$ , at least one carbon atom separates  $Y$  and the  $-NH-$  or  $-S-$  of  $Z$ , wherein, under conditions for peptide synthesis, functional groups of  $Z$  are protected;
- $SS$  is a solid support;
- wherein said derivatized resin represented by formula (I) is prepared by a process comprising the steps of:
- (i) reacting a starting material represented by formula (C)
- (C)  $R_1-(C=X)-Y-Z-SS$ , wherein  $R_1$  is a leaving group;
- with a reactant of formula (D)
- (D)  $R_4-NH_2$
- to form the product (I) of formula  $R_4-NH-(C=X)-Y-Z-SS$ ; and
- (ii) recovering the derivatized resin (I).

1 2. The method according to claim 1 which further comprises reacting an aldehyde or  
2 ketoamide with the derivatized resin represented by formula (I), thereby producing an  
3 immobilized aldehyde or ketoamide.

1 3. The method according to claim 2, further comprising the step of performing solid-  
2 phase chemistry on said immobilized aldehyde or ketoamide, selected from peptide  
3 synthesis, synthesis of peptide analogs, production of a peptidomimetic compound and  
4 combinatorial chemistry, thereby producing a modified aldehyde or ketoamide, wherein  
5 reactive groups present on a growing peptide or peptide analog chain or peptidomimetic  
6 compound are optionally protected.

1 4. The method according to claim 3, further comprising the step of cleaving,  
2 deprotecting and recovering the modified aldehyde or ketoamide as the free aldehyde or  
3 ketoamide.

1 5. The method according to claim 2, further comprising the step of cleaving,  
2 deprotecting and recovering the aldehyde or ketoamide as the free aldehyde or ketoamide.

1 6. The method according to claim 1, wherein said material represented by formula  
2 (C) is prepared by a process comprising reacting a starting material of formula

3 (A)  $R-Y-Z-SS$ , wherein R is a leaving group,

4 with a reactant of formula

5 (B)  $R_1-(C=X)-R_2$ , wherein R<sub>2</sub> is a leaving group, same or different  
6 than R<sub>1</sub>,

7 to form said starting material (C) represented by formula

8 (C)  $R_1-(C=X)-Y-Z-SS$ .

1 7. The method according to claim 6 wherein -R-Y of reactant (A) is  $-NH_2$ , such that  
2 said method produces a derivatized resin represented by formula (IA):

3 (IA)  $R_4-NH-(C=X)-NH-Z-SS$ .

1 8. The method according to claim 6 wherein Y is absent or is  $-\text{CH}_2-$ , X is oxygen,  
2 and R1 is hydroxyl, such that said method produces a derivatized resin represented by  
3 formula (IB):

4 (IB)  $\text{R}_4\text{-NH-(C=O)-Y-Z-SS}$ .

1 9. The method according to claim 8 which further comprises thionating the  
2 derivatized resin (IB) to produce a product represented by formula (IC);

3 (IC)  $\text{R}_4\text{-NH-(C=S)-Y-Z-SS}$ .

1 10. The method according to claim 9 wherein said thionating comprises contacting  
2 the product (IB) with Lawesson's reagent or  $\text{P}_2\text{S}_5$  in mild base.

1 11. The method according to claim 9 further comprising alkylating the derivatized  
2 resin (IC) with an alkylating agent capable of contributing an alkyl group R11 to form an  
3 intermediate represented by the formula (H):

4 (H)  $\text{R}_4\text{-N=(C-S-R11)-Y-Z-SS}$ , and reacting the intermediate (H) with  $\text{NH}_2\text{-}$   
5  $\text{R}_7$  to form a product represented by the formula (ID):

6 (ID)  $\text{R}_4\text{-NH-(C=NR}_7\text{)-Y-Z-SS}$ ; and recovering the product (ID).

1 12. The method according to claim 11 wherein said alkylating agent is selected from  
2 the group consisting of iodomethane, iodoethane, methylbromide, ethylbromide,  
3 allylbromide, allylchloride, dimethylsulfate, and  $\text{CH}_3\text{OSO}_3\text{CF}_3$ .

1 13. The method according to claim 1 to produce a product represented by the formula  
2 (ID), wherein reactant (C), when Y is not absent and R1 is  $-\text{OH}$ , is prepared by a process  
3 comprising:

4 reacting a starting material represented by formula (B):

5 (B)  $\text{R}_1\text{-(C=X)-R}_2$ , wherein R1 is  $-\text{OH}$  and R2 is an independently selected  
6 leaving group, same or different than R1, and X is  $\text{NR}_7$ ,

7 with a reactant represented by formula (G):

8 (G) T-Z-SS; wherein T is -CH<sub>2</sub>Cl, -NH<sub>2</sub>, or -COOH, under conditions  
 9 permitting reaction of (B) with (C), such that T is transformed into moiety Y, and  
 10 recovering the material (C) wherein X is NR<sub>7</sub>.

1 14. The method according to claim 13 wherein the reactant (B) is selected from the  
 2 group consisting of diimidazole imine and phosgeneimine diimidazole.

1 15. The method according to claim 1 wherein, when R<sub>4</sub> of the derivatized resin  
 2 represented by formula (I) is R<sub>3</sub>-NH, R<sub>4</sub> is converted to a reactive derivatized resin  
 3 bearing a free amine by removal of R<sub>3</sub>.

1 16. The method according to claim 15 wherein said reactive derivatized resin is  
 2 contacted with an appropriately protected aldehyde or ketoamide to form a semicarbazone  
 3 derivatized resin.

1 17. The method according to claim 16 wherein said aldehyde is an argininal having a  
 2 guanidino side chain and an amino terminal nitrogen.

1 18. The method according to claim 17 wherein said aldehyde is orthogonally  
 2 protected.

1 19. The method according to claim 18 wherein said argininal guanidino side chain is  
 2 di-Boc or di-Alloc protected and said amino terminal nitrogen is Fmoc protected.

1 20. The method according to claim 19 further comprising:  
 2 (a) deprotecting said amino terminal nitrogen;  
 3 (b) linking amino acid residues, amino acid analog residues, peptide or peptide analogs to  
 4 said nitrogen to form an immobilized peptide or peptide analog comprising said  
 5 aldehyde at the carboxy terminus thereof; and

6 (c) in a single step, deprotecting and cleaving said immobilized peptide or peptide analog  
7 from said resin.

1 21. The method according to claim 20 wherein said single step deprotecting and  
2 cleaving comprises contacting the immobilized peptide or peptide analog and said resin  
3 with trifluoroacetic acid/water for a time between about one hour and about two hours.

1 22. The method according to claim 16 wherein said semicarbazone derivatized resin  
2 is represented by the formula (II):

3 (II)  $\text{PG-NH-C(R}^*)\text{-CH=N-NH-(C=X)-Y-Z-SS,}$   
4 wherein (R\*) represents an amino acid side chain and PG represents a protecting group.

1 23. The method according to claim 22 wherein a peptide or peptide analog is  
2 synthesized on said semicarbazone derivatized resin by removal of the protecting group,  
3 PG, and linking amino acids, amino acid analogs, peptide or peptide analogs to the free  
4 amino group revealed upon removal of said protecting group PG, to produce a derivatized  
5 resin represented by formula (III):

6 (III)  $(\text{res})_t\text{-NH-C(R}^*)\text{-CH=N-NH-(C=X)-Y-Z-SS,}$   
7 wherein (res)<sub>t</sub> represents a peptide chain of "t" residues, wherein "t" is an integer between  
8 1 and about 50.

1 24. The method according to claim 23 wherein t is an integer between about 3 and 10.

1 25. The method according to claim 23 wherein said (res)<sub>t</sub> is produced by sequential  
2 linkage of monomers or by linkage of one or more oligomeric or polymeric units.

1 26. The method according to claim 23 wherein said derivatized resin represented by  
2 formula (III) is selected from the group consisting of:

3  $(\text{res})_t\text{-NH-C(R}^*)\text{-CH=N-NH-(C=X)-NH-Z-SS;}$   
4  $(\text{res})_t\text{-NH-C(R}^*)\text{-CH=N-NH-(C=X)-NH-SS;}$

- 5 (res)<sub>t</sub>-NH-C(R\*)-CH=N-NH-(C=O)-CH<sub>2</sub>-Z-SS;  
 6 (res)<sub>t</sub>-NH-C(R\*)-CH=N-NH-(C=O)-Z-SS;  
 7 (res)<sub>t</sub>-NH-C(R\*)-CH=N-NH-(C=O)-SS;  
 8 (res)<sub>t</sub>-NH-C(R\*)-CH=N-NH-(C=S)-CH<sub>2</sub>-Z-SS;  
 9 (res)<sub>t</sub>-NH-C(R\*)-CH=N-NH-(C=S)-Z-SS;  
 10 (res)<sub>t</sub>-NH-C(R\*)-CH=N-NH-(C=S)-SS;  
 11 (res)<sub>t</sub>-NH-C(R\*)-CH=N-NH-(C=NR<sub>7</sub>)-CH<sub>2</sub>-Z-SS;  
 12 (res)<sub>t</sub>-NH-C(R\*)-CH=N-NH-(C=NR<sub>7</sub>)-Z-SS; and  
 13 (res)<sub>t</sub>-NH-C(R\*)-CH=N-NH-(C=NR<sub>7</sub>)-SS.

1 27. The method according to claim 26 wherein the moiety (res)<sub>t</sub>-NH-C(R\*)-CH=  
 2 represents a resin linked protease inhibitor.

1 28. The method according to claim 2 wherein said reacting is for purpose of purifying  
 2 or isolating an aldehyde- or a ketoamide-containing compound wherein said reacting  
 3 comprises:

4 (i) contacting, under conditions permitting interaction of said aldehyde or  
 5 ketoamide carbonyl in solution with a free amino-terminal amine of a  
 6 derivatized resin of formula:

7 (I) NH<sub>2</sub>-NH-(C=X)-Y-Z-SS; and

8 (b) allowing sufficient time for said interaction to proceed to completion such  
 9 that said aldehyde or ketoamide is bound to said derivatized resin thereby  
 10 removing the aldehyde- or ketoamide-containing compound from the  
 11 solution.

1 29. The method according to claim 3 comprising preparation of a library of peptides  
 2 or peptide analogs comprising the steps of:

3 (i) in each of a series of separate reaction vessels, contacting an aldehyde or  
 4 ketoamide with a derivatized resin represented by formula (I), under conditions which  
 5 permit the formation of a stable semicarbazone between said aldehyde or ketoamide and

6 said resin, thereby producing an immobilized aldehyde or ketoamide as the P<sub>1</sub> residue of a  
7 nascent peptide or peptide analog;

8 (ii) in each of said series of separate reaction vessels, contacting same or  
9 different amino acid residues or amino acid analog residues with the thus immobilized  
10 aldehyde or ketoamide under conditions permitting formation of a peptide bond so as to  
11 produce a series of P<sub>2</sub> residues, same or different, in each of said series of separate  
12 reaction vessels; and

13 (iii) repeating step (ii) as many times as required so as to produce a sequential  
14 series of P residues to generate a peptide or peptide analog of the desired number of  
15 residues, with intermediate steps of protection and deprotection of reactive groups present  
16 on the growing peptide or peptide analog chain, as required.

1 30. The method according to claim 6 wherein R<sub>1</sub> is selected from the group  
2 consisting of imidazole, p-nitrophenoxy, Cl, succinimidyl, and Me-imidazolium; R<sub>2</sub> is  
3 selected from the group consisting of imidazole, Cl, succinimidyl, and Me-imidazolium.

1 31. The method according to claim 30 wherein reactant (A) is selected from the group  
2 consisting of aminomethylated polystyrene resin and 4-methyl benzhydramine resin.

1 32. A method for production of a derivatized resin represented by the formula (I):

2 (I) R<sub>4</sub>-NH-(C=X)-Y-Z-SS wherein:

3 R<sub>4</sub> is -NH-R<sub>3</sub>, -NH<sub>2</sub>, -OH, or -O-R<sub>3</sub>, wherein R<sub>3</sub> is a protecting  
4 group, provided that when R<sub>4</sub> is -NH-R<sub>3</sub> or -O-R<sub>3</sub>, then the  
5 protecting group is removed and replaced by -H in the final product  
6 (I);

7 X is O, S, or NR<sub>7</sub>;

8 R<sub>7</sub> is H, alkyl, alkenyl, aryl, aralkyl, cycloalkyl, or heterocycle;

9 Y is absent, -NH-, or -CH<sub>2</sub>-;

10 Z is absent or is a substituent selected from the group consisting of

11 -NH-, -O-, -(C=O)-, -S-, SO<sub>2</sub>-, alkyl, alkenyl, aryl, aralkyl,  
 12 cycloalkyl, heterocycle, and combinations thereof, provided that  
 13 when Y is absent and X is O or S, Z does not comprise -(C=O)-  
 14 immediately adjacent to -(C=X)-, and when Y is -NH- and Z  
 15 comprises an -NH- or an -S-, at least one carbon atom separates Y  
 16 and the -NH- or -S- of Z, wherein, under conditions for peptide  
 17 synthesis, functional groups of Z are protected;

18 SS is a solid support;

19 wherein said derivatized resin represented by formula (I) is prepared by a process  
 20 comprising the steps of:

21 (i) reacting a starting material of formula

22 (E) R<sub>4</sub>-NH-(C=X)-R<sub>2</sub>, wherein R<sub>2</sub> is a leaving group,

23 with a reactant of formula

24 (A) R-Y-Z-SS, wherein R is a leaving group,

25 to form the derivatized resin (I) of formula R<sub>4</sub>-NH-(C=X)-Y-Z-SS; and

26 (iii) recovering the derivatized resin (I).

1 33. The method according to claim 32 which further comprises reacting an aldehyde  
 2 or ketoamide with the derivatized resin represented by formula (I), thereby producing an  
 3 immobilized aldehyde or ketoamide.

1 34. The method according to claim 33, further comprising the step of performing  
 2 solid-phase chemistry on said immobilized aldehyde or ketoamide, selected from peptide  
 3 synthesis, synthesis of peptide analogs, production of a peptidomimetic compound and  
 4 combinatorial chemistry, thereby producing a modified aldehyde or ketoamide, wherein  
 5 reactive groups present on a growing peptide or peptide analog chain or peptidomimetic  
 6 compound are optionally protected.

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- 1 35. The method according to claim 34, further comprising the step of cleaving,  
2 deprotecting and recovering the modified aldehyde or ketoamide as the free aldehyde or  
3 ketoamide.
- 1 36. The method according to claim 33, further comprising the step of cleaving,  
2 deprotecting and recovering the aldehyde or ketoamide as the free aldehyde or ketoamide.
- 1 37. The method according to claim 32 wherein said reactant (E) is prepared by a  
2 process comprising the steps of:
- 3 (i) reacting a starting material of formula  
4 (B)  $R1-(C=X)-R2$ , wherein R1 and R2 are independently selected  
5 leaving groups, same or different,  
6 with a reactant of  
7 (D)  $R4-NH_2$   
8 to form said reactant (E) of formula  
9 (E)  $R4-NH-(C=X)-R2$ ; and recovering the reactant (E).
- 1 38. The method according to claim 32 wherein derivatized resin (I) is prepared by a  
2 process wherein, when X of reactant (B) is an oxygen, said oxygen in the derivatized  
3 resin (I)  $R4-NH-(C=O)-Y-Z-SS$  is converted to sulfur by thionation to produce  
4 derivatized resin (I) of formula  $R4-NH-(C=S)-Y-Z-SS$  and, optionally, alkylating said  
5 derivatized resin of formula  $R4-NH-(C=S)-Y-Z-SS$  and thereafter contacting with  $NH_2-$   
6  $R7$ , to produce derivatized resin (I) of formula  $R4-NH-(C=NR7)-Y-Z-SS$ .
- 1 39. The method according to claim 32 wherein, when  $R4$  of the derivatized resin  
2 represented by formula (I) is  $R3-NH$ ,  $R4$  is converted to a reactive derivatized resin  
3 bearing a free amine by removal of  $R3$ .

1 40. The method according to claim 39 wherein said reactive derivatized resin is  
2 contacted with an appropriately protected aldehyde or ketoamide to form a semicarbazone  
3 derivatized resin.

1 41. The method according to claim 40 wherein said aldehyde is an argininal having a  
2 guanidino side chain and an amino terminal nitrogen.

1 42. The method according to claim 41 wherein said aldehyde is orthogonally  
2 protected.

1 43. The method according to claim 42 wherein said argininal guanidino side chain is  
2 di-Boc or di-Alloc protected and said amino terminal nitrogen is Fmoc protected.

1 44. The method according to claim 43 further comprising:  
2 (a) deprotecting said amino terminal nitrogen;  
3 (b) linking amino acid residues, amino acid analog residues, peptide or peptide analogs to  
4 said nitrogen to form an immobilized peptide or peptide analog comprising said  
5 aldehyde at the carboxy terminus thereof; and  
6 (c) in a single step, deprotecting and cleaving said immobilized peptide or peptide analog  
7 from said resin.

1 45. The method according to claim 44 wherein said single step deprotecting and  
2 cleaving comprises contacting the immobilized peptide or peptide analog and said resin  
3 with trifluoroacetic acid/water for a time between about one hour and about two hours.

1 46. The method according to claim 40 wherein said semicarbazone derivatized resin  
2 is represented by the formula (II):

3 (II)  $\text{PG-NH-C(R}^*)\text{-CH=N-NH-(C=X)-Y-Z-SS,}$

4 wherein (R<sup>\*</sup>) represents an amino acid side chain and PG represents a protecting group.

1 47. The method according to claim 46 wherein a peptide or peptide analog is  
 2 synthesized on said semicarbazone derivatized resin by removal of the protecting group  
 3 PG and linking amino acids, amino acid analogs, peptide or peptide analogs to the free  
 4 amino group revealed upon removal of said protecting group PG, to produce a derivatized  
 5 resin represented by formula (III):

6 (III)  $(\text{res})_t\text{-NH-C(R}^*)\text{-CH=N-NH-(C=X)-Y-Z-SS}$ ,

7 wherein  $(\text{res})_t$  represents a peptide chain of "t" residues, wherein "t" is an integer between  
 8 about 1 and about 50.

1 48. The method according to claim 48 wherein t is an integer between about 3 and 10.

1 49. The method according to claim 46 wherein said  $(\text{res})_t$  is produced by sequential  
 2 linkage of monomers or by linkage of one or more oligomeric or polymeric units.

1 50. The method according to claim 47 wherein said derivatized resin represented by  
 2 formula (III) is selected from the group consisting of:

3  $(\text{res})_t\text{-NH-C(R}^*)\text{-CH=N-NH-(C=X)-NH-Z-SS}$ ;

4  $(\text{res})_t\text{-NH-C(R}^*)\text{-CH=N-NH-(C=X)-NH-SS}$ ;

5  $(\text{res})_t\text{-NH-C(R}^*)\text{-CH=N-NH-(C=O)-CH}_2\text{-Z-SS}$ ;

6  $(\text{res})_t\text{-NH-C(R}^*)\text{-CH=N-NH-(C=O)-Z-SS}$ ;

7  $(\text{res})_t\text{-NH-C(R}^*)\text{-CH=N-NH-(C=O)-SS}$ ;

8  $(\text{res})_t\text{-NH-C(R}^*)\text{-CH=N-NH-(C=S)-CH}_2\text{-Z-SS}$ ;

9  $(\text{res})_t\text{-NH-C(R}^*)\text{-CH=N-NH-(C=S)-Z-SS}$ ;

10  $(\text{res})_t\text{-NH-C(R}^*)\text{-CH=N-NH-(C=S)-SS}$ ;

11  $(\text{res})_t\text{-NH-C(R}^*)\text{-CH=N-NH-(C=NR}_7\text{)-CH}_2\text{-Z-SS}$ ;

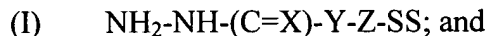
12  $(\text{res})_t\text{-NH-C(R}^*)\text{-CH=N-NH-(C=NR}_7\text{)-Z-SS}$ ; and

13  $(\text{res})_t\text{-NH-C(R}^*)\text{-CH=N-NH-(C=NR}_7\text{)-SS}$ .

1 51. The method according to claim 50 wherein  $(\text{res})_t\text{-NH-C(R}^*)\text{-CH=}$  represents a  
 2 resin linked protease inhibitor.

52. The method according to claim 33 wherein said reacting is for the purpose of purifying or isolating an aldehyde- or a ketoamide-containing compound, wherein said reacting comprises:

- (i) contacting, under conditions permitting interaction of said aldehyde or ketoamide carbonyl in solution with a free amino-terminal amine of a derivatized resin of formula:



- (b) allowing sufficient time for said interaction to proceed to completion such that said aldehyde or ketoamide is bound to said derivatized resin thereby removing the aldehyde- or ketoamide-containing compound from the solution.

53. The method according to claim 34 comprising preparation of a library of peptides or peptide analogs comprising the steps of:

- (i) in each of a series of separate reaction vessels, contacting an aldehyde or ketoamide with a derivatized resin represented by formula (I), under conditions which permit the formation of a stable semicarbazone between said aldehyde or ketoamide and said resin, thereby producing an immobilized aldehyde or ketoamide as the P<sub>1</sub> residue of a nascent peptide or peptide analog;

- (ii) in each of said series of separate reaction vessels, contacting same or different amino acid residues or amino acid analog residues with the thus immobilized aldehyde or ketoamide under conditions permitting formation of a peptide bond so as to produce a series of P<sub>2</sub> residues, same or different, in each of said series of separate reaction vessels; and

- (iii) repeating step (ii) as many times as required so as to produce a sequential series of P residues to generate a peptide or peptide analog of the desired number of residues, with intermediate steps of protection and deprotection of reactive groups present on the growing peptide or peptide analog chain, as required.

1 54. The method according to claim 37 wherein R1 is selected from the group  
 2 consisting of imidazole, p-nitrophenoxy, Cl, succinimidyl, and Me-imidazolium; R2 is  
 3 selected from the group consisting of imidazole, Cl, succinimidyl, and Me-imidazolium.

1 55. The method according to claim 32 wherein reactant (A) is selected from the group  
 2 consisting of aminomethylated polystyrene resin and 4-methyl benzhydrylamine resin.

1 56. A method for production of a derivatized resin represented by the formula (I):

2 (I)  $R_4-NH-(C=X)-Y-Z-SS$

3 wherein:

4  $R_4$  is  $-NH-R_3$ ,  $-NH_2$ ,  $-OH$ , or  $-O-R_3$ , wherein  $R_3$  is a protecting  
 5 group, provided that when  $R_4$  is  $-NH-R_3$  or  $-O-R_3$ , then the  
 6 protecting group is removed and replaced by  $-H$  in the final product  
 7 (I);

8  $X$  is O, S, or NR7;

9  $R_7$  is H, alkyl, alkenyl, aryl, aralkyl, cycloalkyl, or heterocycle;

10  $Y$  is absent,  $-NH-$ , or  $-CH_2-$ ;

11  $Z$  is absent or is a substituent selected from the group consisting of  
 12  $-NH-$ ,  $-O-$ ,  $-(C=O)-$ ,  $-S-$ ,  $SO_2-$ , alkyl, alkenyl, aryl, aralkyl,  
 13 cycloalkyl, heterocycle, and combinations thereof, provided that  
 14 when  $Y$  is absent and  $X$  is O or S,  $Z$  does not comprise  $-(C=O)-$   
 15 immediately adjacent to  $-(C=X)-$ , and when  $Y$  is  $-NH-$  and  $Z$   
 16 comprises an  $-NH-$  or an  $-S-$ , at least one carbon atom separates  $Y$   
 17 and the  $-NH-$  or  $-S-$  of  $Z$ , wherein, under conditions for peptide  
 18 synthesis, functional groups of  $Z$  are protected;

19  $SS$  is a solid support;

20 said method comprising the steps of:

21 (i) reacting a starting material of formula

22 (AA)  $R_4-N=C=X$ ,

23 with the an anion of formula (BB):

- 24 (BB) (-)Y-Z-SS,  
25 and quenching the reaction with a proton source; and  
26 (ii) recovering the derivatized resin (I).

1 57. The method according to claim 56 wherein said proton source is a strong or weak  
2 acid, selected from the group consisting of water, HCl, and acetic acid.

1 58. The method according to claim 56 wherein the anion Y(-) in reactant (BB) is  
2 generated by treatment of Y with a base selected from the group consisting of: sodium or  
3 potassium hydride, sodium potassium or lithium alkoxide (e.g. ethoxide), potassium tert-  
4 butoxide, lithium diisopropyl amide, and lithium or potassium bis(trimethylsilyl) amide.

1 59. The method according to claim 56 which further comprises reacting an aldehyde  
2 or ketoamide with the derivatized resin represented by formula (I), thereby producing an  
3 immobilized aldehyde or ketoamide.

1 60. The method according to claim 59, further comprising the step of performing  
2 solid-phase chemistry on said immobilized aldehyde or ketoamide, selected from peptide  
3 synthesis, synthesis of peptide analogs, production of a peptidomimetic compound and  
4 combinatorial chemistry, thereby producing a modified aldehyde or ketoamide, wherein  
5 reactive groups present on a growing peptide or peptide analog chain or peptidomimetic  
6 compound are optionally protected.

1 61. The method according to claim 60, further comprising the step of cleaving,  
2 deprotecting and recovering the modified aldehyde or ketoamide as the free aldehyde or  
3 ketoamide.

1 62. The method according to claim 59, further comprising the step of cleaving,  
2 deprotecting and recovering the aldehyde or ketoamide as the free aldehyde or ketoamide.

- 1 63. The method according to claim 56 wherein, when X is oxygen, the reactant (AA)  
2 is an isocyanate, when X is sulfur, the reactant (AA) is thiocyanate, and where X is NR7,  
3 the reactant (AA) is a carbodiimide.
- 1 64. The method according to claim 56 wherein, when R4 of the derivatized resin  
2 represented by formula (I) is R3-NH, R4 is converted to a reactive derivatized resin  
3 bearing a free amine by removal of R3.
- 1 65. The method according to claim 64 wherein said reactive derivatized resin is  
2 contacted with an appropriately protected aldehyde or ketoamide to form a semicarbazone  
3 derivatized resin.
- 1 66. The method according to claim 65 wherein said aldehyde is an argininal having a  
2 guanidino side chain and an amino terminal nitrogen.
- 1 67. The method according to claim 66 wherein said aldehyde is orthogonally  
2 protected.
- 1 68. The method according to claim 67 wherein said argininal guanidino side chain is  
2 di-Boc or di-Alloc protected and said amino terminal nitrogen is Fmoc protected.
- 1 69. The method according to claim 68 further comprising:  
2 (a) deprotecting said amino terminal nitrogen;  
3 (b) linking amino acid residues, amino acid analog residues, peptide or peptide analogs to  
4 said nitrogen to form an immobilized peptide or peptide analog comprising said  
5 aldehyde at the carboxy terminus thereof; and  
6 (c) in a single step, deprotecting and cleaving said immobilized peptide or peptide analog  
7 from said resin.

1 70. The method according to claim 69, wherein said single step deprotecting and  
2 cleaving comprises contacting the immobilized peptide or peptide analog and said resin  
3 with trifluoroacetic acid/water for a time between about one hour and about two hours.

1 71. The method according to claim 65 wherein said semicarbazone derivatized resin  
2 is represented by the formula (II):

3 (II)  $\text{PG-NH-C(R}^*)\text{-CH=N-NH-(C=X)-Y-Z-SS,}$

4 wherein (R<sup>\*</sup>) represents an amino acid side chain and PG represents a protecting group.

1 72. The method according to claim 70 wherein a peptide or peptide analog is  
2 synthesized on said semicarbazone derivatized resin by removal of the protecting group  
3 PG and linking amino acids, amino acid analogs, peptide or peptide analogs to the free  
4 amino group revealed upon removal of said protecting group PG, to produce a derivatized  
5 resin represented by formula (III):

6 (III)  $(\text{res})_t\text{-NH-C(R}^*)\text{-CH=N-NH-(C=X)-Y-Z-SS,}$

7 wherein (res)<sub>t</sub> represents a peptide chain of "t" residues, wherein "t" is an integer between  
8 1 and about 50.

1 73. The method according to claim 72 wherein t is an integer between about 3 and 10.

1 74. The method according to claim 72 wherein said (res)<sub>t</sub> is produced by sequential  
2 linkage of monomers or by linkage of one or more oligomeric or polymeric units.

1 75. The method according to claim 72 wherein said derivatized resin represented by  
2 formula (III) is selected from the group consisting of:

3  $(\text{res})_t\text{-NH-C(R}^*)\text{-CH=N-NH-(C=X)-NH-Z-SS;}$

4  $(\text{res})_t\text{-NH-C(R}^*)\text{-CH=N-NH-(C=X)-NH-SS;}$

5  $(\text{res})_t\text{-NH-C(R}^*)\text{-CH=N-NH-(C=O)-CH}_2\text{-Z-SS;}$

6  $(\text{res})_t\text{-NH-C(R}^*)\text{-CH=N-NH-(C=O)-Z-SS;}$

7  $(\text{res})_t\text{-NH-C(R}^*)\text{-CH=N-NH-(C=O)-SS;}$

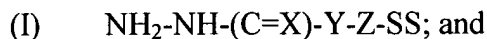


- 8 (res)<sub>t</sub>-NH-C(R\*)-CH=N-NH-(C=S)-CH<sub>2</sub>-Z-SS;  
 9 (res)<sub>t</sub>-NH-C(R\*)-CH=N-NH-(C=S)-Z-SS;  
 10 (res)<sub>t</sub>-NH-C(R\*)-CH=N-NH-(C=S)-SS;  
 11 (res)<sub>t</sub>-NH-C(R\*)-CH=N-NH-(C=NR<sub>7</sub>)-CH<sub>2</sub>-Z-SS;  
 12 (res)<sub>t</sub>-NH-C(R\*)-CH=N-NH-(C=NR<sub>7</sub>)-Z-SS; and  
 13 (res)<sub>t</sub>-NH-C(R\*)-CH=N-NH-(C=NR<sub>7</sub>)-SS.

1 76. The method according to claim 75 wherein (res)<sub>t</sub>-NH-C(R\*)-CH= represents a  
 2 resin-bound protease inhibitor.

1 77. The method according to claim 59 wherein said reacting is for purpose of  
 2 purifying or isolating an aldehyde- or a ketoamide-containing compound, wherein said  
 3 reacting comprises:

- 4 (i) contacting, under conditions permitting interaction of said aldehyde or  
 5 ketoamide carbonyl in solution with a free amino-terminal amine of a  
 6 derivatized resin of formula:



- 8 (b) allowing sufficient time for said interaction to proceed to completion such  
 9 that said aldehyde or ketoamide is bound to said derivatized resin thereby  
 10 removing the aldehyde- or ketoamide-containing compound from the  
 11 solution.

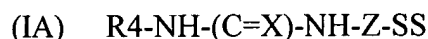
1 78. The method according to claim 60 comprising preparation of a library of peptides  
 2 or peptide analogs comprising the steps of:

- 3 (i) in each of a series of separate reaction vessels, contacting an aldehyde or  
 4 ketoamide with a derivatized resin represented by formula (I), under conditions which  
 5 permit the formation of a stable semicarbazone between said aldehyde or ketoamide and  
 6 said resin, thereby producing an immobilized aldehyde or ketoamide as the P<sub>1</sub> residue of a  
 7 nascent peptide or peptide analog;

(ii) in each of said series of separate reaction vessels, contacting same or different amino acid residues or amino acid analog residues with the thus immobilized aldehyde or ketoamide under conditions permitting formation of a peptide bond so as to produce a series of P<sub>2</sub> residues, same or different, in each of said series of separate reaction vessels; and

(iii) repeating step (ii) as many times as required so as to produce a sequential series of P residues to generate a peptide or peptide analog of the desired number of residues, with intermediate steps of protection and deprotection of reactive groups present on the growing peptide or peptide analog chain, as required.

79. A method for production of a derivatized resin represented by the formula (IA):



wherein:

R<sub>4</sub> is -NH-R<sub>3</sub>, -NH<sub>2</sub>, -OH, or -O-R<sub>3</sub>, wherein R<sub>3</sub> is a protecting group, provided that when R<sub>4</sub> is -NH-R<sub>3</sub> or -O-R<sub>3</sub>, then the protecting group is removed and replaced by -H in the final product (IA);

X is O, S, or NR<sub>7</sub>;

R<sub>7</sub> is H, alkyl, alkenyl, aryl, aralkyl, cycloalkyl, or heterocycle;

Z is absent or is a substituent selected from the group consisting of -NH-, -O-, -(C=O)-, -S-, SO<sub>2</sub>-, alkyl, alkenyl, aryl, aralkyl, cycloalkyl, heterocycle, and combinations thereof, provided that when Z comprises an -NH- or an -S-, at least one carbon atom separates said -NH- or -S-, and the -NH- immediately adjacent to the -(C=X)-, wherein, under conditions for peptide synthesis, functional groups of Z are protected; and

SS is a solid support;

said method comprising the steps of:

(i) reacting a starting material of formula :



21 with a reactant of formula:

22 (F)  $R_4-NH-(C=X)-NH-Q$ ;

23 to form the derivatized resin (IA);

24 (ii) recovering the derivatized resin (IA);

25 wherein:

26 T is  $-CH_2Cl$ ,  $-NH_2$ , or  $-COOH$ , and

27 Q is  $-R_9-R_{10}$ , wherein  $R_9$  is substituted or unsubstituted, alkyl, alkenyl, aryl, aralkyl,

28 cycloalkyl and heterocycle, and  $R_{10}$  is a functional group selected from the group

29 consisting of  $-NH_2$ ,  $-OH$ ,  $-COOH$ ,  $-COCl$ ,  $-SH$ ,  $-SO_2Cl$ ,  $-SO_2H$ ,  $-SO_3$ -lower alkyl,

30 provided that the terminal hydrogen, halogen or a reactive moiety of  $R_{10}$  may be replaced

31 or protected by a protecting group,  $-R_8$ , and moiety Q is selected such that the terminal

32 substituent thereof is reactive with the terminal substituent of T within reactant (G),

33 permitting bond formation between (G) and (F), upon contact thereof.

34

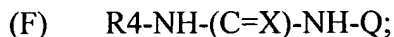
1 80. The method according to claim 79 which further comprises reacting an aldehyde  
2 or ketoamide with the derivatized resin represented by formula (I), thereby producing an  
3 immobilized aldehyde or ketoamide.

1 81. The method according to claim 80, further comprising the step of performing  
2 solid-phase chemistry on said immobilized aldehyde or ketoamide, selected from peptide  
3 synthesis, synthesis of peptide analogs, production of a peptidomimetic compound and  
4 combinatorial chemistry, thereby producing a modified aldehyde or ketoamide, wherein  
5 reactive groups present on a growing peptide or peptide analog chain or peptidomimetic  
6 compound are optionally protected.

1 82. The method according to claim 81, further comprising the step of cleaving,  
2 deprotecting and recovering the modified aldehyde or ketoamide as the free aldehyde or  
3 ketoamide.

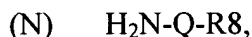
1 83. The method according to claim 80, further comprising the step of cleaving,  
2 deprotecting and recovering the aldehyde or ketoamide as the free aldehyde or ketoamide.

1 84. The method according to claim 79 wherein reactant (F) of formula:

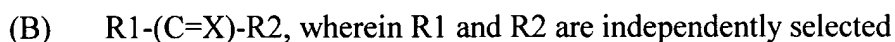


3 is prepared by a process comprising:

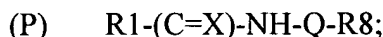
4 (i) reacting a starting material (N) of formula:



6 with a reactant (B) of formula:



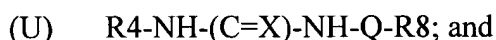
8 leaving groups, same or different, to form an intermediate (P) of formula:



10 (ii) reacting intermediate (P) with reactant (D) of formula

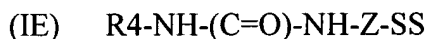


12 to form an intermediate (U) of formula:



14 (iii) removing  $R_8$  to form reactant (F), and recovering reactant (F).

1 85. The method according to claim 79 wherein X is oxygen, and the derivatized resin  
2 is represented by formula (IE):



4 comprising the steps of:

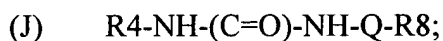
5 (i) reacting a starting material of formula (W):



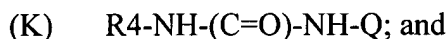
7 with reactant (D) of formula



9 to form intermediate (J) of formula:



11 (ii) removing  $R_8$  from intermediate (J) to form intermediate (K) of formula:



13 (iii) reacting the intermediate (K) with starting material (G) of formula:

14 (G) T-Z-SS to form the derivatized resin (IE) of formula:

15 (IE) R4-NH-(C=O)-NH-Z-SS.

1 86. The method according to claim 85 for preparing a derivatized resin represented by  
2 formula (IF):

3 (IF) R4-NH-(C=S)-NH-Z-SS

4 said method comprising, prior to removal of R8 from intermediate (J):

5 (i) thionating intermediate (J) to form intermediate (L) of formula:

6 (L) R4-NH-(C=S)-NH-Q-R8;

7 (ii) removing R8 from intermediate (L); and

8 (iii) reacting deprotected reactant (L) with reactant (G) T-Z-SS to form derivatized  
9 resin (IF) wherein X is sulfur.

1 87. The method according to claim 86 for preparing a derivatized resin represented by  
2 formula (IG):

3 (IG) R4-NH-(C=NR7)-NH-Z-SS

4 said method comprising the step of, prior to deprotection of intermediate (L) in step (ii) of  
5 claim 86:

6 (i) contacting reactant (L) with an alkylating agent capable of contributing an  
7 alkyl group R11 to form intermediate (M) of formula:

8 (M) R4-N=(C-S-R11)-Q-R8;

9 (ii) reacting intermediate (M) with reactant (H) of formula:

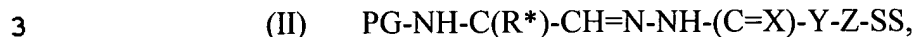
10 (H) NH<sub>2</sub>-R7;

11 (iii) deprotecting and contacting the product with T-Z-SS (G) to form the  
12 derivatized resin of formula (IG), wherein X is NR7.

1 88. The method according to claim 87 wherein said alkylating agent is selected from  
2 the group consisting of iodomethane, iodoethane, methylbromide, ethylbromide,  
3 allylbromide, allylchloride, dimethylsulfate, and CH<sub>3</sub>OSO<sub>2</sub>CF<sub>3</sub>.

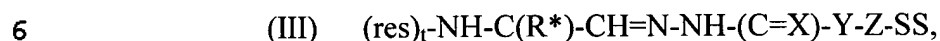
- 1 89. The method according to claim 79 wherein, when R4 of the derivatized resin  
2 represented by formula (I) is R3-NH, R4 is converted to a reactive derivatized resin  
3 bearing a free amine by removal of R3.
- 1 90. The method according to claim 89 wherein said reactive derivatized resin is  
2 contacted with an appropriately protected aldehyde or ketoamide to form a semicarbazone  
3 derivatized resin.
- 1 91. The method according to claim 90 wherein said aldehyde is an argininal having a  
2 guanidino side chain and an amino terminal nitrogen.
- 1 92. The method according to claim 91 wherein said aldehyde is orthogonally  
2 protected.
- 1 93. The method according to claim 92 wherein said argininal guanidino side chain is  
2 di-Boc or di-Alloc protected and said amino terminal nitrogen is Fmoc protected.
- 1 94. The method according to claim 93 further comprising:  
2 (a) deprotecting said amino terminal nitrogen;  
3 (b) linking amino acid residues, amino acid analog residues, peptide or peptide analogs  
4 are to said nitrogen to form an immobilized peptide or peptide analog comprising said  
5 aldehyde at the carboxy terminus thereof; and  
6 (c) in a single step, deprotecting and cleaving said immobilized peptide or peptide analog  
7 from said resin.
- 1 95. The method according to claim 94 wherein said single step deprotecting and  
2 cleaving comprises contacting the immobilized peptide or peptide analog and said resin  
3 with trifluoroacetic acid/water for a time between about one hour and about two hours.

1 96. The method according to claim 90 wherein said semicarbazone derivatized resin  
2 is represented by the formula (II):



4 wherein (R<sup>\*</sup>) represents an amino acid side chain and PG represents a protecting group.

1 97. The method according to claim 96 wherein a peptide or peptide analog is  
2 synthesized on said semicarbazone derivatized resin by removal of the protecting group  
3 PG and linking amino acids, amino acid analogs, peptide or peptide analogs to the free  
4 amino group revealed upon removal of said protecting group PG, to produce a derivatized  
5 resin represented by formula (III):

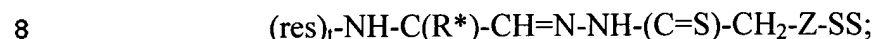
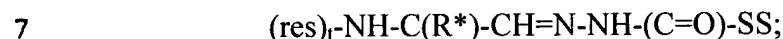
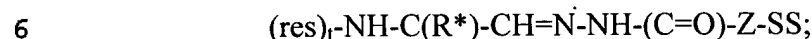
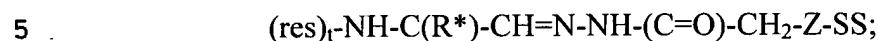


7 wherein (res)<sub>t</sub> represents a peptide chain of "t" residues, wherein "t" is an integer between  
8 about 1 and about 50.

1 98. The method according to claim 97 wherein t is an integer between about 3 and 10.

1 99. The method according to claim 98 wherein said (res)<sub>t</sub> is produced by sequential  
2 linkage of monomers or by linkage of one or more oligomeric or polymeric units.

1 100. The method according to claim 97 wherein said derivatized resin represented by  
2 formula (III) is selected from the group consisting of:



12 (res)<sub>t</sub>-NH-C(R\*)-CH=N-NH-(C=NR7)-Z-SS; and  
 13 (res)<sub>t</sub>-NH-C(R\*)-CH=N-NH-(C=NR7)-SS.

1 101. The method according to claim 100 wherein (res)<sub>t</sub>-NH-C(R\*)-CH= represents a  
 2 resin-bound protease inhibitor.

1 102. The method according to claim 80 wherein said reacting is for purpose of  
 2 purifying or isolating an aldehyde- or a ketoamide-containing compound, wherein said  
 3 reacting comprises:

4 (i) contacting, under conditions permitting interaction of said aldehyde or  
 5 ketoamide carbonyl in solution with a free amino-terminal amine of a  
 6 derivatized resin of formula:

7 (I) NH<sub>2</sub>-NH-(C=X)-Y-Z-SS; and

8 (b) allowing sufficient time for said interaction to proceed to completion such  
 9 that said aldehyde or ketoamide is bound to said derivatized resin thereby  
 10 removing the aldehyde- or ketoamide-containing compound from the  
 11 solution.

1 103. The method according to claim 81 comprising preparation of a library of peptides  
 2 or peptide analogs comprising the steps of:

3 (i) in each of a series of separate reaction vessels, contacting an aldehyde or  
 4 ketoamide with a derivatized resin represented by formula (I), under conditions which  
 5 permit the formation of a stable semicarbazone between said aldehyde or ketoamide and  
 6 said resin, thereby producing an immobilized aldehyde or ketoamide as the P<sub>1</sub> residue of a  
 7 nascent peptide or peptide analog;

8 (ii) in each of said series of separate reaction vessels, contacting same or  
 9 different amino acid residues or amino acid analog residues with the thus immobilized  
 10 aldehyde or ketoamide under conditions permitting formation of a peptide bond so as to  
 11 produce a series of P<sub>2</sub> residues, same or different, in each of said series of separate  
 12 reaction vessels; and



13 (iii) repeating step (ii) as many times as required so as to produce a sequential  
14 series of P residues to generate a peptide or peptide analog of the desired number of  
15 residues, with intermediate steps of protection and deprotection of reactive groups present  
16 on the growing peptide or peptide analog chain, as required.

1 104. The method according to claim 84 wherein R1 is selected from the group  
2 consisting of imidazole, p-nitrophenoxy, Cl, succinimidyl, and Me-imidazolium; R2 is  
3 selected from the group consisting of imidazole, Cl, succinimidyl, and Me-imidazolium.

1 105. The method according to claim 79 wherein reactant (G) is selected from the group  
2 consisting of aminomethylated polystyrene resin and 4-methyl benzhydrylamine resin.

1 106. A method for preparing a derivatized resin which comprises:  
2 (i) contacting an amino methylated polystyrene resin with 1,1-carbonyldiimidazole in  
3 dimethylformamide;  
4 (ii) contacting the product of step (i) with hydrazine in N,N-dimethylformamide; and  
5 (iii) recovering the deprotected, derivatized resin.

1 107. The method according to claim 106, further comprising contacting the derivatized  
2 resin with a di-Boc side-chain-protected, Fmoc amino-protected argininal, or a di-Alloc  
3 side-chain-protected, Boc amino-protected argininal to produce a protected immobilized  
4 argininal.

1 108. The method according to claim 107, further comprising conducting solid phase  
2 peptide synthesis on the protected immobilized argininal, by removing the amino  
3 protection and reaction of activated amino acids or peptides with the deprotected amino  
4 group of the immobilized argininal to produce an immobilized peptide comprising an  
5 argininal at the carboxy terminus thereof.

1 109. The method according to claim 108, further comprising, in a single step,  
2 deprotecting and cleaving the immobilized peptide from the resin, thereby releasing the  
3 immobilized peptide comprising an argininal at the carboxy terminus thereof.

1 110. The method according to claim 109 wherein said single step deprotecting and  
2 cleaving comprises contacting the immobilized peptide or peptide analog and said resin  
3 with trifluoroacetic acid/water for a time between about one hour and about two hours.

1 111. A method for preparing a derivatized resin which comprises:  
2 (i) contacting 1,1-carbonyldiimidazole in dimethylformamide with t-butylcarbazate;  
3 (ii) contacting the product of step (i) with amino methylated polystyrene resin under an  
4 atmosphere of nitrogen;  
5 (iii) removing the t-butyl protection by treatment with trifluoroacetic acid in  
6 dichloromethane in the presence of thioanisole under a nitrogen atmosphere; and  
7 (iv) recovering the deprotected, derivatized resin.

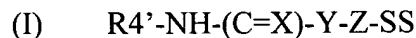
1 112. The method according to claim 111, further comprising contacting the derivatized  
2 resin with a di-Boc side-chain-protected, Fmoc amino-protected argininal, or a di-Alloc  
3 side-chain-protected, Boc amino-protected argininal to produce a protected immobilized  
4 argininal.

1 113. The method according to claim 112, further comprising conducting solid phase  
2 peptide synthesis on the protected immobilized argininal, by removing the amino  
3 protection and reaction of activated amino acids or peptides with the deprotected amino  
4 group of the immobilized argininal to produce an immobilized peptide comprising an  
5 argininal at the carboxy terminus thereof.

1 114. The method according to claim 113, further comprising, in a single step,  
2 deprotecting and cleaving the immobilized peptide from the resin, thereby releasing the  
3 immobilized peptide comprising an argininal at the carboxy terminus thereof.

115. The method according to claim 114 wherein said single step deprotecting and cleaving comprises contacting the immobilized peptide or peptide analog and said resin with trifluoroacetic acid/water for a time between about one hour and about two hours.

116. A method for production of an hydroxamic ester, which comprises preparing a solid support of formula:



wherein:

$R4'$  is -OH, or -OR<sub>3</sub>, wherein R<sub>3</sub> is a protecting group, provided that when  $R4'$  is -OR<sub>3</sub>, then the protecting group is removed and replaced by -H in the final derivatized resin (I);

X is O, S, or NR<sub>7</sub>;

R<sub>7</sub> is H, alkyl, alkenyl, aryl, aralkyl, cycloalkyl, or heterocycle;

Y absent, -NH-, -CH<sub>2</sub>-;

Z is absent or is a substituent selected from the group consisting of -NH-, -O-, -(C=O)-, -S-, SO<sub>2</sub>-, alkyl, alkenyl, aryl, aralkyl, cycloalkyl, heterocycle, and combinations thereof, provided that when Y is -NH-, if Z comprises an -NH- or a -S-, at least one carbon atom separates Y and Z;

SS is a solid support;

said method comprising the steps of:

(i) reacting a starting material of formula:

(C)  $R1-(C=X)-Y-Z-SS$ , wherein R<sub>1</sub> and R<sub>2</sub> are independently selected leaving groups, same or different, with a reactant of formula:



to form the derivatized resin (I);

(ii) recovering the derivatized resin (I); and

(iii) esterifying the resin at the free amino hydroxyl group.